

Ezetimibe (Zetia®) Does not Add Benefit to Simvastatin (Zocor®) Monotherapy: Review of the ENHANCE Trial

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The results of the ENHANCE trial were published in the *New England Journal of Medicine* in April of this year.¹ Upon release of the study results at the American College of Cardiology and internet publication by *NEJM*, the lay press called the study a "flop"² because ezetimibe (Zetia®) did not reduce atherosclerosis as anticipated based on the drug's lipid-lowering effect.

Patients with familial hypercholesterolemia were randomized to receive simvastatin 80 mg daily with ezetimibe 10 mg daily or placebo. After 24 months, combination therapy reduced the mean LDL-cholesterol from 319 mg/dL to 141.3 mg/dL; monotherapy reduced LDL cholesterol from 317.8 mg/dL to 192.7 mg/dL. The between group difference was statistically significant ($P < 0.01$). In contrast, the mean change in carotid-artery intima-media thickness was not different between groups.¹

The study investigators proposed three explanations for the lack of change in carotid-artery intima-thickness with ezetimibe:¹

- 1) By inhibiting HMG-CoA, the statin agents not only lower cholesterol, but may also improve endothelial function and exhibit anti-inflammatory activity.
- 2) The measurement technique did not accurately capture changes in atherosclerotic burden.
- 3) Patients with familial hypercholesterolemia are treated early and aggressively with high-dose statin

therapy. It is possible that the patients enrolled in the study had already been on significant lipid-lowering therapy and that disease progression had already been slowed substantially prior to study enrollment.

The investigators dismissed the non-lipid-lowering effects of ezetimibe and the potential for poor measurements of atherosclerotic burden, and ultimately stated that the reason for the seeming inconsistencies in the results remains unknown.¹

The significance of this trial is further emphasized by the publication of two accompanying editorials.^{3,4} According to one of these, the assumption can no longer be made that the lower the LDL-cholesterol level is will correlate with clinical or imaging benefits as has been the case with statins and resins.³ Another states that an outcome study of simvastatin in combination with ezetimibe is underway but results of this study are not expected until 2011.⁴ Both editorials conclude that other lipid-lowering agents such as the statins should be used preferentially over ezetimibe and that ezetimibe should be reserved for patient that cannot tolerate high dose statins, fibrates, or niacin⁴ or cannot meet their target LDL cholesterol goals with these agents.³

Since no outcome data has been published previously with ezetimibe and substantial data exists for improvement in clinical outcomes with the statins, one might suspect that this data will have little effect on practice. However, over 3.1 million prescriptions for ezetimibe or ezetimibe combined with simvastatin were filled in December of 2006⁷ according to

Jackevicius, et al.⁵ Since October 2002, the prescription volume of ezetimibe (Zetia[®]) in the United States has climbed by an average of 27,200 per month to 1,360,000 per month by December 2006. Similarly, the prescription volume of ezetimibe plus simvastatin (Vytorin[®]) increased by an average of 61,000 per month to 1,776,000 per month by December of 2006 since July 2004.⁵

With no demonstrated benefit on clinical outcomes what is responsible for the rapid market growth of these products? Jackevicius, et al. compared the prescription volume in the United States to that in Canada. In 2006 the ratio of statin prescriptions to ezetimibe prescription was 26:1 in Canada and 5:1 in the United States. Factors that may have influenced the difference in prescribing patterns may be a longer approval time for ezetimibe in Canada, lack of approval for a combination product in Canada, formulary restrictions on the use of ezetimibe in some Canadian provinces, and the lack of direct-to-consumer advertising in Canada.⁵

The first three concerns are data driven to varying extents and require the agent to prove its value to an educated audience. In contrast, direct-to-consumer advertising relies on the patient to initiate a discussion of the product with the health care provider. In 2007, over \$200 million was spent on direct to-consumer advertising for Vytorin[®]⁵ -- a product with no proven benefit in clinical outcomes over generic simvastatin in light of the ENHANCE study.

So where does that leave us -- exactly where we should be if we are dedicated to initiating therapy with the most cost-effective therapy with proven benefit. Ezetimibe should be reserved for those who are intolerant to other lipid lowering agents until outcome data supporting its clinical benefit are available.

References

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Best wishes to...

*Provost Dan McAlexander
Dean Jack Williams
Dean Phil Johnston
Associate Dean Eric Hobson*

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ACPE Council
on
June 19, 2008
as the final
step in the
application process.*

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